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PATENT
Docket No.: **19603/468 (CRF D-1595C)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Barany et al.
Serial No.	:	08/794,851
Filed	:	February 4, 1997
For	:	DETECTION OF NUCLEIC ACID SEQUENCE DIFFERENCES USING THE LIGASE DETECTION REACTION WITH ADDRESSABLE ARRAYS

Examiner:
P. Ponnaluri

Art Unit:
1627

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REQUEST FOR RECONSIDERATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the July 10, 2001, office action, applicants respectfully request reconsideration.

The rejection of claims 1-43, 45-66, 75-80, 82-88, and 138-151 under the judicially-created doctrine of obviousness-type double patenting over claims 1-28 of U.S. Patent No. 6,027,889 to Barany et. al., ("'889 patent") is respectfully traversed.

The present application was filed on February 4, 1997, and claims benefit of the February 9, 1996, filing date of U.S. Provisional Patent Application Serial No. 60/011,359. The '889 patent issued from U.S. Patent Application Serial No. 08/864,473, filed May 28, 1997, and claims benefit of the May 29, 1996, filing date for U.S. Provisional Patent Application Serial No. 60/018,532. Applicants thus submit that the present application has an earlier effective filing date than that of the '889 patent. As a result, withdrawal of the double patenting rejection and permitting the present application to issue without a terminal disclaimer will not cause the present application to have a term which is longer than that of the '889 patent.

The '889 patent claims a method of identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences. This method involves carrying

out a ligase detection reaction ("LDR") step followed by a polymerase chain reaction ("PCR") procedure. A method utilizing this sequence of steps is nowhere disclosed or claimed in the present application. Further, in the LDR/PCR process of the '889 patent, the oligonucleotide probes used in carrying out the LDR procedure respectively have a 5' upstream primer-specific portion and 3' downstream primer-specific portion which are present in the LDR products if the target nucleotide sequence is present in the sample being tested. For the subsequent PCR stage, the oligonucleotide primers include an upstream primer containing the same 5' upstream primer-specific portion of the ligation product and a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product. As a result, the downstream primer hybridizes, in the first cycle, to the 3' downstream primer-specific portion of the ligation product and, in subsequent cycles, the upstream primer hybridizes to the 5' upstream primer-specific portion of the extension product complementary to the ligation product sequence, and the 3' downstream portion of the ligation product sequence hybridizes to the 3' downstream portion of the ligation product. Nowhere does the present application teach or claim the specific structure of either the oligonucleotide probes used for LDR or the oligonucleotide primers for PCR, let alone the interrelated nature of that structure.

It is well settled that an obvious-type double patenting rejection cannot be made where the claimed invention of a first patent would not have been an obvious variant of the claimed invention of a second patent application. See In re Vogel, 422 F.2d 438, 164 U.S.P.Q. 645 (CCPA 1970). As set forth in Section 804 of the Manual of Patent Examining Procedure ("MPEP"), "the first question to be asked is—does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent?" Here, the answer to this question is clearly "No". For the reasons noted above, there would have been no suggestion in the present application of a method involving an LDR procedure followed by a PCR stage, let alone the specific structure of the oligonucleotide probes and primers used to carry out this method. Accordingly, the claimed invention of the '889 patent can hardly be deemed an obvious variation of that claimed here.

The question has arisen with regard to whether the issue of obviousness-type double patenting should be resolved through a one-way test or a two-way test. Only a one-way analysis is conducted where the application at issue is the later-filed application or both are filed on the same day. MPEP § 804, para. II.B.1.(a). This provision of the MPEP does

not govern here, because, as noted above, the present application has an earlier effective filing than that of the '889 patent. In such circumstances, MPEP § 804, para. II.B.1.(a). states the following:

> Similarly, even if the application at issue is the earlier filed application, only a one—way determination of obviousness is needed to support a double patenting rejection in the absence of a finding of: (A) administrative delay on the part of the Office causing delay in prosecution of the earlier filed application; and (B) applicant could not have filed the conflicting claims in a single (i.e. the earlier filed) application. See MPEP § 804, paragraph II.B.1.(b) below. (emphasis added).

Utilizing this test, it is clear that the two—way determination of obviousness must be carried out here.

As to step (A) of above test, the following passage from MPEP § 804 is instructive:

> Similarly, where, through no fault of the applicant, the claims in a later filed application issue first, an obvious-type double patenting rejection is improper, in the absence of a two-way obviousness determination, because the applicant does not have complete control over the rate of progress of a patent application through the Office.

A review of the prosecution histories of the '889 patent and the present application demonstrate beyond dispute that the application corresponding the '889 patent was rapidly processed to issuance by the U.S. Patent and Trademark Office (PTO"), while the present application encountered significant delay. In particular, the '889 patent issued after only one office action and one response to it. By contrast, progress of the present application in the PTO has been much slower due to the imposition of numerous office actions rejecting the claims on various differing grounds. To date, there have been 6 full office actions on the merits and 2 advisory actions. In response, applicants have now had to file 9 amendments and/or requests for reconsideration; 3 interviews have been held. All of this was precipitated by repeated changes in position by the previous examiner. The present situation where: there were many offic actions, often with different grounds for rejections and the office actions

were fully and substantively responded to, in writing and at interviews, is precisely the scenario where the two-way test should be applied due to administrative delay by the PTO. By contrast, In re Emert, 124 F.3d 1458, 44 U.S.P.Q.2d 1149 (Fed. Cir. 1997) is cited by MPEP § 804 as the type of circumstance where there was no administrative delay, because applicant, after receiving an obviousness rejection, did not file a substantive response but chose to repeatedly allow the case to go abandoned in favor of a continuation application. Under the circumstances of the present case, it is beyond question that administrative delay by the PTO caused the present application's issuance to be delayed well beyond that of the application corresponding to the '889 patent.

It is also clear that step (B) of the above test has been satisfied here. As noted *supra*, the claimed subject matter of the '889 patent is nowhere disclosed or claimed in the present application. Contrary to what is stated in the outstanding office action, the claimed subject matter of the '889 patent is not made patentable over the claims of the present application by simply adding a PCR step in the latter. There are other significant differences in process sequence and oligonucleotide probe/primer structure, as fully described above. Accordingly, it would not have been possible to have incorporated claims 1-28 of the '889 patent in the present application.

For all of these reasons, it is clear that the two-way determination of obviousness must be satisfied in order to maintain an obviousness-type double patenting rejection against the pending claims of the present application over claims 1-28 of the '889 patent. MPEP 804, para. II.B.1.(b) provides the following guidance on how to carry out this test:

> When making a two—way obviousness determination where appropriate, it is necessary to apply the *Graham* obviousness analysis twice, once with the application claims as the claims in issue, and once with the patent claims as the claims in issue. Where a two—way obviousness determination is required, an obvious—type double patenting rejection is appropriate only where each analysis compels a conclusion that the invention defined in the claims in issue is an obvious variation of the invention defined in a claim in the other application/patent.

As noted above, the claimed invention of the '889 patent calls for a step sequence and oligonucleotide probe/primer structure which would nowhere be suggested to one of ordinary

skill in the art familiar with the claimed invention. Since this aspect alone of the two—way analysis cannot be satisfied, it is clear that the obviousness-type double patent rejection over claims 1-28 of the '889 patent must be withdrawn.

The rejection of claims 1-43, 45-66, 75-80, 82-88, and 138-151 under the judicially-created doctrine of obviousness-type double patenting over claims 29-54 of U.S. Patent Application Serial No. 09/440,523 to Barany, et. al., ("'523 application") is respectfully traversed.

The '523 application, which issued on July 31, 2001 as U.S. Patent No. 6,268,148, is a division of U.S. Patent Application Serial No. 08/864,473 from which the '889 patent issued. Thus, it is submitted that the claims of the '523 application, like those of the '889 patent are entitled to benefit of May 28, 1996, as an effective filing date which, as noted *supra*, is after that of the present application.

Like the claims of the '889 patent, the claims of the '523 application are very different than those of the present application and call for subject matter which is nowhere disclosed in the present application.

Claims 29-50 of the '523 application call for a method of identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences. This method involves carrying out a first PCR procedure which is followed by a second PCR procedure and then an LDR phase. A method utilizing this sequence of steps is nowhere disclosed or claimed in the present application. Further, the oligonucleotide primers used in carrying out the first PCR procedure respectively have 5' upstream secondary primer-specific portions which are present in the extension products of this first PCR procedure. For the subsequent PCR stage, the oligonucleotide primers include the same sequences as the 5' upstream portions used in the first PCR procedure so these primers for the subsequent PCR stage hybirdize to and amplify the extension products of the first PCR phase. The LDR stage has oligonucleotide probes with portions specific to the extension products of the second PCR stage. Nowhere does the present application teach or claim the specific structure of either the oligonucleotide probes used for LDR or the oligonucleotide primers for PCR, let alone the interrelated nature of that structure.

Claims 51-54 of the '523 application call for a method of identifying two or more of a plurality of sequences differing by one or more single-base changes, insertions,

deletions, or translocations in a plurality of target nucleotide sequences. This method involves carrying out a first PCR procedure which is followed by a second PCR procedure. A method utilizing this sequence of steps is nowhere disclosed or claimed in the present application. Further, the oligonucleotide primers used in carrying out the first PCR procedure respectively have 5' upstream secondary primer-specific portions which are present in the extension products of this first PCR procedure. For the subsequent PCR stage, the oligonucleotide primers include the same sequences as the 5' upstream portions used in the first PCR procedure so these primers for the subsequent PCR stage hybirdize to and amplify the extension products of the first PCR phase. Nowhere does the present application teach or claim the specific structure of the oligonucleotide primers for PCR, let alone the interrelated nature of that structure.

Like the '889 patent, the '523 application issued after 1 PTO office action on the merits and 1 response. Therefore, for substantially the same reasons noted above, a two—way analysis must be carried out to determine whether the claims of the present application are properly rejected for obviousness-type double patenting over claims 29-54 of the '523 application.

As noted *supra*, the claimed subject matter of the '523 application is nowhere disclosed or claimed in the present application. Contrary to what is stated in the outstanding office action, the claimed subject matter of the '523 application is not made patentable from the claims of the present application by simply adding a PCR step in the latter. There are other significant differences in process sequence and oligonucleotide probe/primer structure, as fully described above. Accordingly, it would not have been possible to have incorporated claims 29-54 of the '523 application in the present application. Further, since this aspect alone of the two—way analysis cannot be satisfied, it is clear that the obviousness-type double patent rejection over claims 29-54 of the '523 application must be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Dated: August 10, 2001

Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603
Telephone: (716) 263-1304
Facsimile: (716) 263-1600

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

8/10/01 Wendy L. Harreld

Date